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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/731,349 | 12/06/2000 | Sreekant Nadkarni | 01-678 | 9200 |

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| EXAMINER |
|---|
| OH, SIMON J |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1615 | 16 |

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/731,349 | NADKARNI ET AL. | |
| | Examiner | Art Unit | |
| | Simon J. Oh | 1615 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *16 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3 and 5-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3 and 5-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7, 8, 11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Papers Received*

Receipt is acknowledged of the applicant's letter, received 26 July 2002 regarding the Information Disclosure Statement, received on 15 April 2002. Receipt is also acknowledged of the applicant's response to the Office Action of 16 July 2002, received on 16 August 2002.

### *Response to Arguments*

Applicant's arguments with respect to Claims 1, 3, and 5-18 have been considered but are moot in view of the new ground(s) of rejection.

### *Claim Rejections - 35 USC § 103*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3, 5-7, 9, 10, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Black (EPO Document No. 0 863 134 A1) in view of Patel *et al.* (U.S. Patent No. 6,248,363 B1), Guess *et al.* (U.S. Patent No. 6,054,455), and Bagchi *et al.* (U.S. Patent No. 5,662,883)

The Black application teaches synthesis of 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl) phenyl)-2-cyclopenten-1-one, a COX-2 inhibitor, and its formulation into a pharmaceutical composition by wet granulation techniques (See Methods A through C and Examples 1 through 2c, all on Pages 11-19). Uses of a composition comprising 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl) phenyl)-2-cyclopenten-1-one through oral administration, preferably in a once-

or twice-a-day treatment are also discussed, as well as the various conditions that such treatment could alleviate (See Page 3, Lines 8-10 and 29-46; and Page 5, Lines 22-29). Specific dosages, ranging from 10 mg to 250 mg, are discussed as well (See Page 5, Line 30 to Page 6, Line 5).

The Black document does not explicitly disclose the exact intended functions of the individual excipients used in the COX-2 inhibitor formulation. Black is silent with respect to the use of valdecoxib in the composition, to the limitation regarding particle size of valdecoxib, and to the specific bioavailbility features of a valdecoxib composition.

The Patel *et al.* patent describes a wide variety of formulations for solid carriers of drugs (See Abstract). Patel *et al.* teaches that various hydrophobic drugs that may be used in the disclosed solid carriers, including COX-2 inhibitors, analgesics, and opioid analgesics, alone or in mixtures thereof (See Column 5, Lines 1-23). A listing of suitable additives is given, including lubricants such as magnesium stearate; binders such as polymeric cellulose derivatives and pre-gelatinized starch; diluents such as lactose and microcrystalline cellulose, and disintegrants such as croscarmellose sodium (See Columns 39-40).

The Guess *et al.* patent is relied upon as a teaching reference, solely in order to illustrate that valdecoxib is known in the prior art, as being among a group of selective COX-2 inhibitors (See Column 33, Lines 17-20).

It would be obvious to one of ordinary skill in the art at the time the invention was made, to combine the teachings of Black, Patel *et al.*, and Guess *et al.* into the invention of the instant application. Black teaches compositions with specific COX-2 inhibitors as the active substance, along with suitable dosages. The benefit of a COX-2 inhibitor composition in a once-a-day formulation is explained as well. Black also teaches how such COX-2 inhibitor compositions

could be used to provide treatment for conditions such as rheumatoid arthritis and osteoarthritis. Patel *et al.* teach the functions of the various excipients used in the COX-2 compositions disclosed in Black. Additionally, it provides functional equivalency between the cellulosic polymer used as a binder in the formulations disclosed in Black with the pre-gelatinized starch claimed by the applicant. An examination of those formulations disclosed in Black will reveal that the quantities of the excipients lie within the ranges presented in Claim 5 (See Black; Examples 2, 2b, and 2c). It is the position of the examiner that the limitations in Claims 1 and 3 drawn to bioavailability features of the claimed invention do not impart a patentably distinct property to the claimed invention. Bagchi *et al.* give a broad teaching regarding the importance of reliable bioavailability in the administration of a drug. In the case of drugs of poor water solubility, such as COX-2 inhibitors as disclosed by Patel *et al.*, bioavailability can be improved by decreasing particle size, thereby increasing the total drug particle surface area. Bagchi *et al.* also disclose that based on the available technology at the time, particle sizes ranging from as low as about 1 micron to about 50 microns may be achieved (See Bagchi *et al.*; Column 1, Lines 10-45). Hence, Bagchi *et al.* disclose merely one way, and the motivation to do so, in which one of ordinary skill in the art can make adjustments in the formulation of drug compositions in order to achieve the desired bioavailability of the active ingredient. It is the position of the examiner that the selection of suitable drug particle sizes, down to particle size ranges claimed by the applicant using technology disclosed in Bagchi *et al.*, for the purpose of manipulating the bioavailability of an active ingredient, is within the purview of one of ordinary skill in the art at the time the claimed invention was made.

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Black in view of Patel *et al.*, Guess *et al.*, Bagchi *et al.*, and Burch *et al.* (WIPO Document No. 99/13799)

The relevance of Black, Patel *et al.*, Guess *et al.*, and Bagchi *et al.* is stated in the above rejection of Claims 1, 3, 5-7, 9, 10, and 18 under 35 U.S.C. 103.

Recalling Patel *et al.*, the patent teaches that various hydrophobic drugs that may be used in the disclosed solid carriers, including COX-2 inhibitors, analgesics, and opioid analgesics, alone or in mixtures thereof (See Column 5, Lines 1-23).

Burch *et al.* disclose the use of a combination of an opioid analgesic with a COX-2 inhibitor (See Abstract). Such a combination is desirable because of a synergistic effect produced by the combination that requires lower doses of both types of drugs, hence producing lower side effects (See Page 7, Lines 3-8).

The use of valdecoxib is not specifically disclosed therein. However, because it is also a COX-2 inhibitor, it is the opinion of the examiner that one of ordinary skill in the art could substitute valdecoxib in place of another COX-2 inhibitor in the drug combination disclosed in Burch *et al.* with a reasonable expectation of success, and would be motivated to do so because of the synergistic combination of COX-2 inhibitors and opioid analgesics as disclosed by Burch *et al.*

Claims 11-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Black in view of Patel *et al.*, Guess *et al.*, Bagchi *et al.*, and Ansel *et al.*

The relevance of Black, Patel *et al.*, Guess *et al.*, and Bagchi *et al.* is stated in the above rejection of Claims 1, 3, 5-7, 9, 10, and 18 under 35 U.S.C. 103.

Recalling Patel *et al.*, the patent lists microcrystalline cellulose in at least two categories of pharmaceutical excipients, as a diluent and as a disintegrant (See Patel *et al.*, Column 40, Lines 23-35). Recalling Black, the document discloses examples of COX-2 inhibitor compositions formulated by wet granulation techniques (See Black; Examples 2, 2b, and 2c).

The Ansel *et al.* reference describes basic steps used in wet granulation techniques (See Pages 209-211), including an optional step wherein a portion of the disintegrant is reserved and added to the granulate prior to compression into tablets, in order to create a double-disintegration action in the tablet (See Page 209, 2nd Column, last paragraph to Page 210, 1st Column, Line 5). Ansel *et al.* also describe the use of a dry binder in the wet granulation process (See Page 210, 2nd Column).

Although it is not explicitly disclosed where in the process a dry binder may be added, it is the position of the examiner that one of ordinary skill in the art would include pre-gelatinized starch early in the wet granulation process by blending it with the other dry ingredients with a reasonable expectation of success. It is also the position of the examiner that one of ordinary skill would be aware of the function of microcrystalline cellulose as both a disintegrant and a diluent, and would therefore, according to the disclosure of Ansel *et al.*, be motivated to reserve a portion of both the microcrystalline cellulose and the pre-gelatinized starch to be added in a step between wet granulation tablet compression. The examiner does not see a patentable distinction between the claimed process and wet granulation processes already known in the art. Therefore, the examiner shifts the burden onto the applicant to give a showing of criticality or unexpected results imparted by the claimed process.

Thus the invention, as a whole, is *prima facie* obvious.

***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Simon J. Oh whose telephone number is (703) 305-3265. The examiner can normally be reached on M-F 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (703) 308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Simon J. Oh
Examiner
Art Unit 1615

sjo
November 18, 2002

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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